

Tri-Point Perspectives in *Endocrine News*

The tri-point perspectives were initiated by The Endocrine Society’s Research Affairs Committee in the fall of 2003 as an editorial



feature that would appeal to all of the Society’s members. The topics, authors and outside reviewers are selected by the committee to deal with subject areas from three different angles—that of the basic researcher, the clinical researcher and the physician in practice. The authors write their articles independently and later work together to coordinate them. The drafts are reviewed by the Research Affairs Committee chairs, by independent experts in the specific topic area and then by the Endocrine News editors and staff for grammar and style.

If you have any comments or questions about the tri-point perspectives feature, please email EndocrineNews@endo-society.org If you would like to submit a Letter to the Editor responding to a tri-point perspective please send your letter to ENLetters@endo-society.org (not longer than 200 words and the editorial staff reserves the right to edit each submission).

DIABETES, HEART DISEASE AND INSULIN RESISTANCE

Diabetes, Heart Disease and Insulin Resistance

Management of Type II Diabetes Mellitus: Should We Target Insulin Resistance in Addition to Better Glycemic Control?



Barry Marc Forman, M.D., Ph.D.



Jean-Pierre Després, Ph.D., FAHA



Francine Ratner Kaufman, M.D.

BASIC RESEARCHER VIEW

Thiazolidinediones and PPAR γ Ligands: Insulin Sensitization and Beyond?

Barry Marc Forman, M.D., Ph.D.

Department of Gene Regulation & Drug Discovery

The Beckman Research Institute at City of Hope National Medical Center

It's been seven years since the first insulin-sensitizing thiazolidinedione (TZD) appeared on the market, and in that time, TZDs have produced a number of surprises. It is now clear that TZDs (e.g. rosiglitazone and pioglitazone) have effects on metabolic disease that extend well beyond glucose lowering.

PPAR γ is thus a “force-multiplier” that allows TZDs to regulate not just a single gene, but large networks of physiologically-related genes.

TZDs are synthetic ligands for the nuclear receptor PPAR γ ^{1,2}. Like most nuclear receptors, PPAR γ binds to specific DNA sequences within its target genes. In the presence of ligand, the receptor undergoes a conformation change that allows the DNA-bound receptor to interact with transcriptional co-activator proteins. This ultimately leads to an increased rate of transcription. PPAR γ is expressed in a number of tissues and modulates the expression of multiple genes within each tissue. PPAR γ is thus a “force-multiplier” that allows TZDs to regulate not just a single gene, but large networks of physiologically-related genes. Herein lies the power of TZDs: whereas many drugs target a single enzyme, TZDs can regulate entire metabolic pathways.

Initial studies demonstrated that PPAR γ is highly expressed in adipose tissue and that TZDs promote adipogenesis *in vitro* and

increase white adipose mass *in vivo*. In fact, it is now clear that TZDs induce a battery of genes that coordinate nearly all steps of adipocyte triglyceride (TG) accumulation including: free fatty acid (FFA) release from circulating very low density lipoproteins, glycerol synthesis, uptake of FFA/glycerol into adipocytes, and induction of

enzymes responsible for converting FFAs/glycerol into the immediate precursors for TG synthesis.

These findings raise a surprising question about TZD action: since obesity is a major risk factor for NIDDM, how can PPAR γ ligands relieve insulin resistance while increasing adiposity? This paradox is partially explained by the observation that TZDs promote a shift of TGs from both visceral fat and peripheral tissues (e.g. skeletal muscle) toward subcutaneous fat³. In effect, TZDs preferentially

These findings raise a surprising question about TZD action: since obesity is a major risk factor for NIDDM, how can PPAR γ ligands relieve insulin resistance while increasing adiposity?

increase adiposity in subcutaneous fat. This is consistent with recent findings that insulin resistance is associated with an over-accumula-

tion of lipids in both visceral adipose depots and within the cells of insulin-resistant peripheral tissues⁴. Preferential responsiveness of subcutaneous fat may reflect a higher level of expression of PPAR γ in this depot. It is also possible that different fat depots display depot-specific differences in their ability to induce certain lipogenic genes.

In addition to adipose tissue, PPAR γ is also expressed in vascular endothelial cells, macrophage/foam cells and vascular smooth muscle. This provides a means for TZDs to act directly on the vasculature. Indeed, PPAR γ ligands raise HDL-cholesterol in NIDDM patients and reduce the number and size of atherosclerotic lesions in several rodent models. The effects on HDL-cholesterol and lesion size are mediated by induction of LXR α , another nuclear receptor that is co-expressed in the macrophage foam cell. LXR α promotes cholesterol efflux from atherosclerotic lesions by coordinately inducing a cholesterol efflux pump (ABCA1) and the HDL-associated cholesterol acceptor apolipoprotein-AI.

In contrast to the role of gene activation in the above processes, TZDs can also repress transcription. The precise mechanism un-

derlying transrepression is unclear. However, the net effect of TZDs is to inhibit the activity of transcription factors (NF-kb, AP-1) that regulate the expression of cytokines and other inflammatory mediators. Thus, TZDs can inhibit the initial inflammatory processes that promote atherosclerosis, including macrophage recruitment/attachment and vascular smooth muscle proliferation⁵. Some of the reported anti-inflammatory effects of

TZDs also reduce blood pressure and several potential mechanisms have been described⁶. For example, TZDs inhibit the expression of endothelin-1, a vasoconstrictive peptide expressed in endothelial cells. TZDs may also promote vasodilation by stimulating the release of nitric oxide from the endothelial cell. More recently, PPAR γ was found to be expressed in renal glomeruli and collecting ducts. Although the targets genes in

Many other genes can be down-regulated by TZDs and it appears that PPAR γ may also be a master regulator of inflammatory gene expression.

TZDs occur via both PPAR γ -dependent and independent pathways. Examples of this dual-mode of regulation include inducible nitric oxide synthase, matrix metalloprotease-9 and cyclooxygenase-2: the promoters of these genes are suppressed via PPAR γ -dependent and -independent mechanisms.

these cells have not been fully elucidated, it is possible that TZD action in the kidney contributes to blood pressure control. However, PPAR γ activity in the kidney may be a double-edged sword. Approximately 5 percent of patients on TZDs develop peripheral or pulmonary edema and preliminary data suggest this

Approximately 5 percent of patients on TZDs develop peripheral or pulmonary edema and preliminary data suggest this could be secondary to TZD-induced sodium retention.

Many other genes can be down-regulated by TZDs and it appears that PPAR γ may also be a master regulator of inflammatory gene expression. However, there is an important cautionary note: many of the reported anti-inflammatory effects require supra-pharmacologic doses of TZDs. Therefore, it is not clear if all the reported effects occur at doses that are relevant to TZD-treated patients.

could be secondary to TZD-induced sodium retention.

Although PPAR γ and its ligands were once uniquely linked to fat homeostasis, it is now clear that they have multiple effects on insulin resistance, atherosclerosis and blood pressure regulation. These ligands have clearly provided many surprises in the past and we should look for this trend to continue. **EN**

REFERENCES

- ¹ Van Citters, G. W. & Forman, B. M. *Molecular links between peroxisome proliferator-activated receptor-gamma and metabolic disease in Diabetes mellitus: a fundamental and clinical test* (eds. Olefsky, J. M., Taylor, S. I. & LeRoith, D.) chapter 29, p. 441 (Lippincott Williams & Wilkins, 2003).
- ² Etgen, G. J., Prince, M. J. & Caro, J. F. *Peroxisome proliferator-activated receptor modulators in Diabetes mellitus: a fundamental and clinical test* (eds. Olefsky, J. M., Taylor, S. I. & LeRoith, D.) chapter 78, p. 1139 (Lippincott Williams & Wilkins, 2003).
- ³ Fonseca, V. *Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med, 2003. 115: p. 42S-48S.*
- ⁴ Houmard, J. A., Tanner, C. J., Yu, C., Cunningham, P. G., Pories, W. J., MacDonald, K. G. & Shulman, G. I. *Effect of weight loss on insulin sensitivity and intramuscular long-chain fatty acyl-CoAs in morbidly obese subjects. Diabetes, 2002. 51: p. 2959-2963.*
- ⁵ Hsueh, W. A. & Law, R. *The central role of fat and effect of peroxisome proliferator-activated receptor-gamma on progression of insulin resistance and cardiovascular disease. Am J Cardiol, 2003. 92: p. 3J-9J.*
- ⁶ Zanchi, A., Chiolero, A., Maillard, M., Nussberger, J., Brunner, H. R. & Burnier, M. *Effects of the peroxisomal proliferator-activated receptor-gamma agonist pioglitazone on renal and hormonal responses to salt in healthy men. J Clin Endocrinol Metab, 2004. 89: p. 1140-1145.*

CLINICAL RESEARCHER VIEW

Managing CHD Risk in Type 2 Diabetes: Improving Insulin Resistance May be as Important as Glycemic Control

Jean-Pierre Després Ph.D., FAHA

Québec Heart Institute, Laval Hospital Research Center, Ste-Foy (Québec),
Canada, Department of Food Sciences and Nutrition,
Laval University, Ste-Foy, Québec, (Canada)

The worldwide prevalence of type 2 diabetes has reached epidemic proportions and there is no evidence that this rapid growth will “plateau” in the coming years^{1,2}. Changes in human behavior and lifestyle observed over the last century, which have promoted a positive energy balance, weight gain and obesity leading to the progressive development of a metabolic disease evolving to glucose intolerance and eventually to frank hyperglycemia, have resulted in a dramatic increase in the incidence of diabetes worldwide. Therefore, there has been a striking parallel increase in the prevalence of obesity and type 2 diabetes^{3,4}.

Because of its high prevalence in our population, the contribution of type 2 diabetes as a major risk factor for cardiovascular disease has received considerable attention from the medical community^{5,6}. It has even been proposed that type 2 diabetes should be considered as an equivalent of coronary heart disease (CHD)^{7,8}. As many complications of type 2 diabetes are related to hyperglycemia, achieving a better glycemic control is obviously a very important therapeutic objective. However, although it is clear that it is clinically important to reduce hemoglobin A1c (HbA1c) levels, there is also increasing evidence that hyperglycemia is not the main factor responsible for the increased CHD risk in type 2 diabetic patients⁹. It has rather been proposed that a

cluster of metabolic complications referred to as the metabolic syndrome, which includes an atherogenic dyslipidemia, an insulin resistance state leading to a disturbed plasma glucose/insulin homeostasis, a thrombotic and inflammatory profile, as well as an endothelial dysfunction, could substantially increase the risk of CHD¹⁰.

Furthermore, the impact of the metabolic syndrome on CHD risk could be largely independent from glycemic control or of the presence/absence of type 2 diabetes¹¹. As the metabolic syndrome is largely a consequence of our “toxic” lifestyle, it has been shown that abdominal obesity, especially visceral obesity, could represent the main correlation of the metabolic syndrome in our population^{8,12}.

The recognition of the metabolic syndrome as a major and prevalent cause of CHD in the recently published National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III)⁸ has generated considerable interest in the medical community. In addition, NCEP-ATP III has proposed simple clinical variables to identify individuals at risk of having the metabolic syndrome. Among the five parameters (waist circumference, triglycerides, high-density lipoprotein (HDL)-cholesterol, fasting glycemia, blood pressure) used to identify carriers of the metabolic syndrome, the introduction of waist circumference rather than the body mass index has been

a giant conceptual leap, recognizing the significant role of abdominal obesity as the most prevalent cause of insulin resistance and of the metabolic syndrome in our affluent, sedentary population. Furthermore, these new guidelines recognize the importance of elevated triglycerides and of reduced HDL-cholesterol concentrations as useful lipid markers for the presence of an atherogenic “dysmetabolic” milieu that is now referred to as the metabolic syndrome.

There is also evidence that the increased CHD risk related to the presence of the metabolic syndrome associated with abdominal obesity and insulin resistance could be partly mediated by metabolic abnormalities that are not currently assessed in daily clinical practice (e.g. insulin, apolipoprotein B, low-density lipoprotein (LDL) size, C-reactive protein, adipokines such as interleukin-6, tumor necrosis factor- α and adiponectin concentrations)¹³. It is therefore suggested that in order to optimally manage CHD risk in type 2 diabetic patients, attention should be given not only to the level of glycemic control, but also to the improvement of insulin resistance and of features of the metabolic syndrome. For the time being, although we know that the metabolic syndrome substantially increases the risk of CHD^{11,14}, we do not know which of its features (insulin resistance/hyperinsulinemia, small LDL particles, reduced

adiponectin levels, increased C-reactive protein, etc.) are critical therapeutic targets for the optimal management of CHD risk in type 2 diabetic patients.

Results of clinical trials conducted on or including type 2 diabetic patients have shown the benefits of reducing blood pressure^{15,16}, and of improving the dyslipidemic profile^{17,18} of these patients. The introduction of insulin sensitizers (PPAR-g agonists) in clinical practice will provide an opportunity to test whether improving in vivo insulin action will slow the progression of atherosclerosis and reduce the risk of cardiovascular events in type 2 diabetes. Thiazolidinediones have been reported to have favourable effects on several features of the metabolic syndrome¹⁹ including inflammation²⁰ and whether such metabolic improvements will translate into cardiovascular benefits beyond the impact of this class of drugs on glycemic control is currently under investigation.

Finally, as abdominal obesity represents the most prevalent form of the metabolic syndrome in our population, waist girth should be considered as one of the key screening tools to track patients with insulin resistance and the metabolic syndrome in clinical practice. Thus, in addition to improving insulin sensitivity and managing hypertension and the dyslipidemic state, clinicians should also consider lowering body weight and reducing the waist girth of their patients as important therapeutic targets^{10,12}.

Unfortunately, we have engineered for our population a toxic sedentary environment and easy access to inexpensive processed foods with high energy density and poor nutritional value. The battle against the epidemic of the metabolic syndrome and type 2 diabetes will not be successfully fought by our current medical system as it will clearly require a multi-disciplinary approach. **EN**

REFERENCES

1. Zimmet PZ. *Diabetes epidemiology as a tool to trigger diabetes research and care*. Diabetologia. 1999;42:499-518.
2. Zimmet P, Shaw J, Murray S, Sicree R. *The diabetes epidemic in full flight: forecasting the future*. Diabetes Voice. 2003;48:12-16.
3. Katzmarzyk PT. *The Canadian obesity epidemic, 1985-1998*. CMAJ. 2002;166:1039-40.
4. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. *The spread of the obesity epidemic in the United States, 1991-1998*. JAMA. 1999;282:1519-22.
5. Lee WL, Cheung AM, Cape D, Zinman B. *Impact of diabetes on coronary artery disease in women and men*. Diabetes Care. 2000;23:962-968.
6. Grundy SM, Benjamin EJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Jr, Sowers JR. *Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association*. Circulation. 1999;100:1134-1146.
7. Friesinger GC, Gavin JA. *Diabetes and the cardiologists: a call to action*. J Am Coll Cardiol. 2000;35:1130-1133.
8. *Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)*. JAMA. 2001;285:2486-97.
9. *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)*. UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53.
10. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. *Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition*. Circulation. 2004;109:433-8.
11. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. *NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older*. Diabetes. 2003;52:1210-1214.
12. Després JP, Lemieux I, Prud'homme D. *Treatment of obesity: need to focus on high risk abdominally obese patients*. BMJ. 2001;322:716-20.
13. Lamarche B, Tchernof A, Mauriège P, Cantin B, Dagenais GR, Lupien PJ, Després JP. *Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease*. JAMA. 1998;279:1955-61.
14. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. *Cardiovascular morbidity and mortality associated with the metabolic syndrome*. Diabetes Care. 2001;24:683-9.
15. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Opåril S, Wedel H, Aurup P, Edelman J, Snapinn S. *Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol*. Lancet. 2002;359:1004-10.
16. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. *Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy*. N Engl J Med. 2001;345:861-9.
17. Collins R, Armitage J, Parish S, Sleight P, Peto R. *MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial*. Lancet. 2003;361:2005-16.
18. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D. *Insulin resistance and cardiovascular events with low HDL cholesterol. The Veterans Affairs HDL Intervention Trial (VA-HIT)*. Diabetes Care. 2003;26:1513-1517.
19. Gurnell M, Savage DB, Chatterjee VK, O'Rahilly S. *The metabolic syndrome: peroxisome proliferator-activated receptor gamma and its therapeutic modulation*. J Clin Endocrinol Metab. 2003;88:2412-21.
20. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. *Effect of rosiglitazone treatment on non-traditional markers of cardiovascular disease in patients with type 2 diabetes mellitus*. Circulation. 2002;106:679-84.

CLINICAL PRACTITIONER VIEW

Insulin Resistance and Type 2 Diabetes in Youth

Francine Ratner Kaufman, M.D.

Professor of Pediatrics, The Keck School of Medicine of USC, Head, the Center for Diabetes, Endocrinology and Metabolism, Childrens Hospital Los Angeles

As reported in 2002, 14 percent of youth in the United States are overweight (BMI \geq 95th percentile for age and gender) and 31.5 percent are at risk for overweight (BMI \geq 85th for age and gender)¹. Insulin resistance occurs in overweight children and youth and is associated with the metabolic syndrome, dyslipidemia, vascular complications, and type 2 diabetes. Type 2 diabetes, which was rare in the early 1990s, now accounts for up to eight – 45 percent of new-onset cases of diabetes in youth².

There are several factors, in addition to overweight, that lead to insulin resistance in the pediatric population. These include: sedentary lifestyle; gender; age; onset of puberty; and genetics, which can be seen as a positive family history of type 2 diabetes and by the propensity for type 2 to occur in certain ethnic groups.

In overweight adolescents, approximately 50 percent of the variance seen in insulin sensitivity is accounted for by adiposity. As in adults, it is visceral fat, rather than total body fat, which correlates with basal and stimulated insulin levels and inversely correlates with insulin sensitivity³. African-American youth are more insulin resistant than Caucasian children. The Bogalusa Heart Study showed that African-American teens were more obese and had higher insulin levels to oral glucose and higher insulin to glucose ratios compared to their Caucasian counterparts⁴. Arslanian has shown lower resting energy expenditure, higher fasting and first

phase insulin levels, and lower insulin sensitivity in African-American subjects⁵. Goran et al, has shown that Hispanic youth are also more insulin resistant compared to Caucasian children⁶.

Puberty is a state of relative insulin resistance and there is an increase in basal and stimulated insulin secretion during the progression through normal puberty⁷. It has been shown that insulin-mediated glucose disposal is on average 30 percent lower in Tanner 2-4 puberty compared to that seen in Tanner 1 children during hyperinsulinemic euglycemic clamp studies. More female youth have type 2 diabetes than adolescent males. The

an overall prevalence of metabolic syndrome in youth to be 4.2 percent; however, this increased to 28 percent in overweight youth¹⁰. Cruz et al¹¹ reported a 30 percent prevalence of metabolic syndrome in overweight youth with a family history of type 2 diabetes, and Weiss et al reported a rate of 50 percent in subjects with severe obesity¹².

Pre-diabetes is common in children and youth, as well as in adults. Evaluation of overweight children and adolescents by Sinha et al¹³ with oral glucose tolerance testing showed 25 percent of children four to 10 years of age and 21 percent of adolescents 11-18 years of age

Puberty is a state of relative insulin resistance and there is an increase in basal and stimulated insulin secretion during the progression through normal puberty⁷.

female:male ratio is 1.7:1. It is hypothesized that this is due to elements of the polycystic ovary syndrome (PCOS)⁸. Physical activity increases insulin sensitivity and overweight youth undergoing regular exercise show a fall in fasting insulin levels that increase again with the return in sedentary lifestyle⁹.

Metabolic syndrome occurs with a high rate in overweight youth. Recent cross-sectional data obtained from National Health and Nutrition Examination Survey III (NHANES III) evaluating 2430 youth between the ages of 12-19 years and using modified National Cholesterol Education Program (NCEP) criteria, found

had impaired glucose tolerance (IGT). The best predictor of IGT was insulin resistance. Goran et al reported IGT in 28 percent of overweight Hispanic youth with a positive family history of type 2 diabetes⁶.

In my experience, the presentation of type 2 diabetes in pediatric subjects is variable. Most of the patients I see are symptomatic from hyperglycemia at the time of diagnosis. In addition, I see many youth with type 2 diabetes who have significant co-morbidities. There are a number of studies that have shown a high prevalence of hypertension and dyslipidemia¹⁴. At present, few studies have been

done to determine the most effective treatment regimens, the role that physical activity and nutrition counseling play in improving glycemic outcome and the most effective ways to reduce cardiovascular risk. If patients are symptomatic from hyperglycemia at diagnosis, I start them on insulin. If they have a glucose level below 250 mg/dl and are relatively

There is little doubt that insulin resistance has a major negative effect clinically.

asymptomatic, I find that Metformin is effective as initial therapy. The occasional child found on screening can try lifestyle changes; however, I find this is rarely beneficial. The *Treatment Options for type 2 Diabetes in Adolescents and Youth* (TODAY) trial, an National Institutes of Health-funded multi-center (12 sites throughout the U.S.) study, was recently launched and will evaluate the glycemic outcome, indicators of insulin resistance and cardiovascular risk factors in youth randomized to one of three treatment modalities (Metformin alone, Metformin plus Rosiglitazone and Metformin) within two years of the diagnosis of type 2 diabetes.

In conclusion, obesity and sedentary lifestyle have a significant impact on the health of children. Low fitness levels, combined with ethnicity and family history of diabetes, are driving the epidemic of insulin resistance in increasingly younger children. With the onset of puberty comes even greater insulin resistance. Depending on the level of fitness, obesity, ethnicity and family history, patients will remain insulin resistant following puberty. The longer the pubertal insulin resistance remains, the greater the chance for the development of dyslipidemia, hypertension and, pre-diabetes and overt type 2 diabetes, which itself, is a risk factor for cardiovascular disease.

There is little doubt that insulin resistance has a major negative effect clinically. Improving insulin resistance should be a goal for those treating youth with obesity, metabolic syndrome, pre-diabetes and diabetes. How best to do this—lifestyle versus pharmacotherapy—has yet to be determined in youth, but should become a research priority. **EN**

REFERENCES

¹ Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA* 2002;288:1728-1732.

² Fagot-Campagna A: Emergence of type 2 diabetes mellitus in children: Epidemiological evidence. *J Pediatr Endocrinol Metab* 2000;13:1395-1402.

³ Caprio S: Insulin resistance in childhood obesity. *J Pediatr Endocrinol Metab* 2002;15:Suppl 1:487-492.

⁴ Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: The Bogalusa Heart Study. *N Engl J Med* 1998;338:1650-1656.

⁵ Arslanian S: Metabolic differences between Caucasians and African-American children and the relationship to type 2 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002;15:509-517.

⁶ Goran MI, Bergman RN, Avila Q, Watkins M, Ball GDC, Shaibi GQ, Weigensberg MJ, et al. Impaired glucose tolerance and reduced beta-cell function in overweight Latino children with a positive family history for type 2 diabetes. *J Clin Endocrinol Metab* 2004;89;

⁷ Caprio S. Insulin resistance in childhood obesity. *J Pediatr Endocrinol Metab* 2002;15:Suppl1:487-492.

⁸ Arslanian SA, Lewy VD, Danadian K: Glucose intolerance in obese adolescents with polycystic ovary syndrome: Roles of insulin resistance and B-cell dysfunction and risk of cardiovascular disease. *J Clin Endocrinol Metab* 2001;86:66-71.

⁹ Ferguson MA, Gutin B, Le NA, Karp W, Litaker M, Humphries M, Okuyama T, Riggs S, Owens S: Effects of exercise training and its cessation on components of the insulin resistance syndrome in obese children. *Int J Obes Relat Metab Disor* 1999;23:889-895.

¹⁰ Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: Findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med.* 2003;157:821-827.

¹¹ Cruz ML, Weigensberg MJ, Huang TT-K, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 2004;89:108-113.

¹² Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362-2374.

¹³ Sinha R, Fisch G, Teague B, Tamborlane W, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802-810.

¹⁴ Arslanian S. Type 2 diabetes in children: Clinical aspects and risk factors. *Horm Res* 2002;57:Suppl 1:19-28.

¹⁵ Bloomgarden ZT. Type 2 diabetes in the young. *Diabetes Care* 2004;27:998-1010.

¹⁶ Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M and the Consensus Workshop Writing Committee. Type 2 diabetes in the young: The evolving epidemic. *Diabetes Care* 2004;27:1798-1811.